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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/526,089	02/23/2005	Cecilia Kepka	PU0265	6639

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EXAMINER	
MAKAR, KIMBERLY A	
ART UNIT	**PAPER NUMBER**
1636	

MAIL DATE	DELIVERY MODE
10/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/526,089	KEPKA ET AL.	
	Examiner	Art Unit	
	Kimberly A. Makar, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,14-18 and 20-22* is/are pending in the application.

4a) Of the above claim(s) *11,12 and 14-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 20-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 February 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/23/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Claims 11-19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 07/25/07.

Applicant's election without traverse of invention I in the reply filed on 7/25/07 is acknowledged.

Oath/Declaration

2. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

> The oath or declaration is defective because:
> It was not executed in accordance with either 37 CFR 1.66 or 1.68.
>
> Non-Initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

3. The oath contains initialed changes to the mailing addresses, however the initials are not associated with anyone of record with the application, and are not dated.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1- 10, and 20-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claim 1 (and dependent claims 2-10, and 22) recites the limitation "the top phase" in claim 1(e). There is insufficient antecedent basis for this limitation in the claim.

7. Claims 20-21 provides for the use of a polymer that exhibits inverse solubility characteristics at a temperature below about 60°C in an aqueous two-phase system for the purification of plasmid DNA from a cell lysate, wherein the copolymer is a copolymer of ethylene oxide and propylene oxide, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

8. Claim 20-21 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1-5, 8-10, 20-22 are rejected under 35 U.S.C. 103(a) as being obvious over Ageland et al (US Patent 6,107, 467) (of record 6/29/07) in view of Ohlsson R, (A rapid method for the isolation of circular DNA using an aqueous two-phase partition system. Nucleic Acids Res. 1978 Feb;5(2):583-90). Claims 1—5, 8-10, 20-22 recite a method of purifying plasmid DNA in a aqueous two phase system, comprising providing a first polymer that exhibits inverse solubility characteristics, a second polymer that is immiscible in the first polymer, and optionally a salt, contacting said composition with an aqueous solution comprising plasmid DNA, providing a phase separation and subsequently isolating the aqueous phase, increasing the temperature of the isolated aqueous phase to a temperature above the cloud point of the first polymer and below a temperature where plasmid DNA is degraded and isolating the aqueous phases so formed, and can optionally be subjected to a chromatography step to recover plasmid DNA from the isolated top phase. The method is limited wherein the first polymer is ethylene oxide and propylene oxide with a cloud point below about 60°C, and the second polymer is dextran, starch or hydroxylated starches. The contacting step involves mixing at room temperature and isolation is by centrifugation. The method

further includes a step in which a cell lysate is desalted prior to contacting the lysate with the composition of the polymers in claim 1. Claims 20-22 recite the use of a polymer that exhibits inverse solubility characteristic at temperatures below 60°C in an aqueous two-phase system for the purification of plasmid DNA from a cell lysate, where the polymer is a copolymer of ethylene oxide and propylene oxide, and wherein the copolymer is 50% propylene oxide and 50% ethylene oxide.

11. Ageland teaches a method of purifying a recombinant ApoA or Apo E protein using a two-phase aqueous system, comprising providing a first copolymer of 50% ethylene oxide and propylene oxide that exhibits inverse solubility characteristics, a second polymer of dextran, or starches that is immiscible in the first polymer, and optionally a salt, contacting said composition with an aqueous solution comprising a bacterial cell lysate including the recombinant Apo A or Apo E, providing a phase separation and subsequently isolating the aqueous phase, increasing the temperature of the isolated aqueous phase to a temperature above the cloud point of the copolymer of 50% ethylene oxide and propylene oxide (below a temperature where plasmid DNA is degraded) and isolating the aqueous phases so formed. Ageland teaches that this two phase system is a replacement of the traditional PEG/dextran systems known in the art.

12. Ageland teaches the first polymer is ethylene oxide and propylene oxide with a cloud point below about 60°C (column 11, lines 15-40), and the second polymer is dextran, starch or hydroxylated starches (column 15, lines 25-32). Ageland teaches that a suitable copolymer is 50% ethylene oxide and 50% ethylene oxide copolymer

(column 12, lines 4-16), in addition to polyglycol ethers and other polymers (column 9, lines 37-67).

13. Ageland teaches that the recombinant Apo proteins can be made through recombinant DNA techniques (column 13, lines 27 through column 15, line 9). Ageland does not specifically teach that the "recombinant DNA technique" comprises the expression of the Apo proteins from a "plasmid DNA." However, the references listed in columns 13-15 inherently disclose Apo proteins produced from plasmid DNA.

14. Ageland teaches that the bacterial cell lysate (which comprises the recombinant Apo proteins, and accompanying plasmid DNA) are added in aqueous phases to the polymer solutions, which is mixed at room temperature, and the phase separation is enhanced by centrifugation (column 7, lines 40-48; column 12 lines 41-56, column 13, lines 48-58), wherein the phases are isolated from each other. The aqueous phase is then raised to a temperature above the cloud point of the first polymer (up to 60°C) which is below a temperature that would degrade DNA) (column 10 line 31- column 11, lines 40).

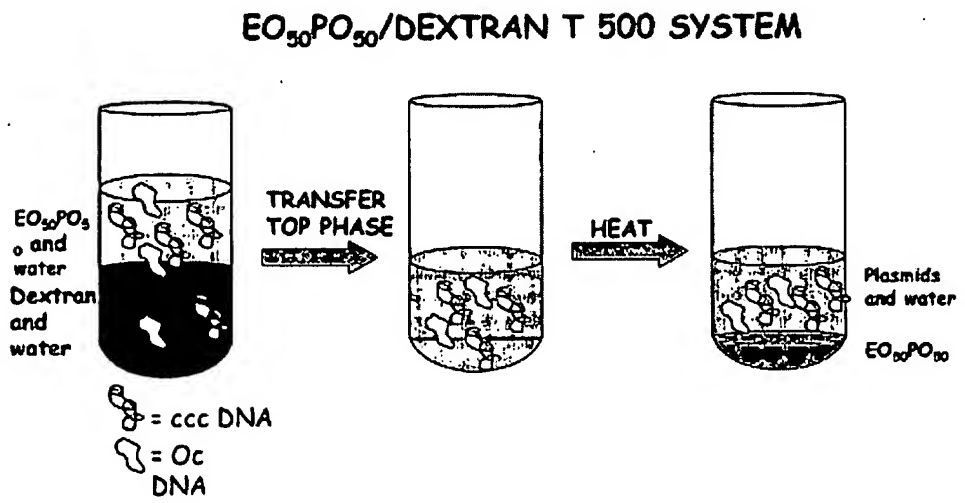
15. The instant specification fails to clearly define "desalting" but does teach methods of desalting:

> A last embodiment of this first aspect is a method for purification of plasmid DNA from a lysate, which comprises a first step of desalting the lysate, a second step for recovery which comprises the method described above, and a last step of chromatography for final purification of the plasmid DNA. The desalting can be performed by any suitable method. In one embodiment, the desalting is performed by a method selected from the group that consists of gel filtration, diafiltration and ultrafiltration (Page 10 of the instant specification).

16. Ageland teaches that two phase separations have been used to purify nucleic acids and proteins (column 1, lines 20-23). Ageland teaches that the compounds to be purified "have been pretreated, e.g. by centrifugation, filtration, ultrafiltration, or flocculation, for removing all or essentially all of the cellular debris (column 13, lines 48-58). And, that "it is preferred that the temperature-induced phase separation is carried out in the essential absence of salt, since this facilitates the subsequent purification of the hydrophobic or amphiphilic compound" (column 11, lines 36-4), and in the example section, he teaches that the *E coli* lysates are subjected to ultrafiltration in order to concentrate the proteins (see column 15, lines 18-24). Absent evidence to the contrary, this step of ultrafiltration inherently also desalts the cellular lysate solution used in the methodology of Ageland.

17. Ageland further teaches that the isolated, and heat treated top phase can be further subjected to a chromatography step (column 10, lines 31-38). Ageland teaches the same steps utilizing the same polymers to purify the Apo protein, as those described in the instant specification summarized by Figure 1 of the instant specification:

Figure 1



18. Compared to figure 1 of Ageland:

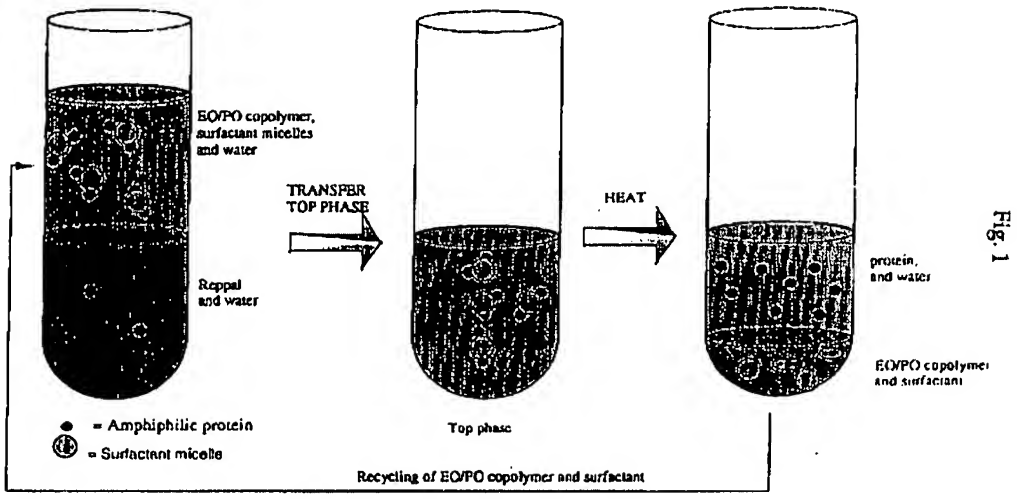


Fig. 1

19. Absent evidence to the contrary, the heated aqueous phase of Ageland would also have the plasmid DNA expressing the recombinant Apo proteins, in addition to the Apo proteins.

20. However, Ageland teaches a method of purifying proteins using the identical methodology of the claims, not a method of purifying Plasmid DNA. Ageland teaches that this method is an improvement of the polyethylene Glycol/Dextran purification protocols, that have well known in the art. Ageland teaches that the methods can be used on nucleic acids.

21. Ohlsson R, (A rapid method for the isolation of circular DNA using an aqueous two-phase partition system. Nucleic Acids Res. 1978 Feb;5(2):583-90) teaches a method of isolating plasmid DNA using a two-phase methodology.

22. It would have been obvious to the skilled artisan to combine the teaching of Ageland on a method of purifying proteins from cell lysates using a method of two-phase separation utilizing copolymers of Ethylene Oxide and Propylene Oxide, which Ageland discloses can be used for nucleic acids with the teaching of Ohlsson on a method of using a two-phase system to purify plasmid DNA and purify plasmid DNA using the methodology of Ageland. All of the claimed elements were known in the prior art, and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable result to one of ordinary skill in the art at the time of the invention (See KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007)).

23.

24. Claims 6-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ageland et al (US Patent 6,107, 467) in view of Ohlsson R, (A rapid method for the

isolation of circular DNA using an aqueous two-phase partition system. Nucleic Acids Res. 1978 Feb;5(2):583-90). Claims 6-7 recite a method of purifying plasmid DNA in a aqueous two phase system, comprising providing a first polymer that exhibits inverse solubility characteristics, a second polymer that is immiscible in the first polymer, and optionally a salt, contacting said composition with an aqueous solution comprising plasmid DNA, providing a phase separation and subsequently isolating the aqueous phase, increasing the temperature of the isolated aqueous phase to a temperature above the cloud point of the first polymer and below a temperature where plasmid DNA is degraded and isolating the aqueous phases so formed wherein the weight ratio of the first polymer to the second polymer is about 1:1, and is about 4.5% of the fist polymer and the second polymer is about 4.5% (w/w) of the composition in claim 1.

25. Ageland and Ohlsson teach a method of purifying plasmid DNA in a aqueous two phase system, comprising providing a first polymer that exhibits inverse solubility characteristics, a second polymer that is immiscible in the first polymer, and optionally a salt, contacting said composition with an aqueous solution comprising plasmid DNA, providing a phase separation and subsequently isolating the aqueous phase, increasing the temperature of the isolated aqueous phase to a temperature above the cloud point of the first polymer and below a temperature where plasmid DNA is degraded and isolating the aqueous phases so formed (see above).

26. Ageland teaches that the ratio of first polymer to second polymer can be from the range of 20:1 to about 1:10, from 10:1 to 1:5, and from 5:1 to 1:2 (column 7, lines 26-31). Ageland further teaches that the concentration of the polymers and the second

polymer is 1-30% by weight, 3-20% by weight and 5-15% by weight (column 7, lines 8-19). Ageland's experiments show the use of the fist polymer and the second polymer is about 4.0% (w/w) of the initial composition. Ageland does not specifically disclose that the weight ratio of the first polymer to the second polymer is about 1:1, and is about 4.5% of the fist polymer and the second polymer is about 4.5% (w/w) of the initial composition.

27. It would have been obvious to the skilled artisan to perform the method using any of the ratios of the polymers by weight, as disclosed by Ageland, in order to maximize the DNA yield with the polymer concentrations wherein the weight ratio of the first polymer to the second polymer is about 1:1, and is about 4.5% of the fist polymer and the second polymer is about 4.5% (w/w) of the initial composition. Thus, an ordinary practitioner would have recognized that the concentrations could be adjusted to maximize the desired results. As noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

28. Routine optimization is not considered inventive and no evidence has been presented that the selection of specific concentrations was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art (see MPEP 2144.05).

29. All of the claimed elements were known in the prior art reference of Ageland and Ohlsson and one of skill in the art could have combined the elements as claimed by

known methods with no change in the respective functions, and the combinations would have yielded predictable results to one of ordinary kill in the art at the time of the invention ((See *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007)). Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the instant invention was made, it must be considered that said ordinary skilled artisan would have had reasonable expectation of success in practicing the claimed invention.

Conclusion

30. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Makar, Ph.D. whose telephone number is 571-272-4139. The examiner can normally be reached on 8AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D. can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Kam/09/24/07

/Daniel M. Sullivan/
Primary Examiner
Art Unit 1636